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The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part 1—A need assessment study

Smita Salunke[a,b,*,1], George Giacoia[c,2], Catherine Tuleu[a,b,1]

[a] Pharmaceutics and Centre for Paediatric, Pharmacy Research, UCL, School of Pharmacy, United Kingdom
[b] European Paediatric Formulation Initiative, United Kingdom
[c] Obstetric and Pediatric Pharmacology Branch (OPPB), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), United Kingdom

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ABSTRACT

Excipients that are commonly used in adult medicines have been associated with elevated toxicological risks and safety issues in children. However, the information available on their acceptability for paediatric age groups is sparse and distributed over various sources. Hence, European (Eu) and United States (US) Paediatric Formulation Initiatives (PFIs) are collaboratively creating a STEP database. Because the development of database is a costly and time consuming venture, it is important to capture the requirements from the potential users and identify at an early stage the content and features that will serve the specific needs so that they can incorporate into the databases as it is developed.

Aim: To assess the need of STEP database, to determine the database content and structure that meets the needs of the potential users.

Method: A global survey was conducted via EuPFI website and email invitations, targeting a representative cross section of industrial, regulatory, academic and clinical professionals, to capture the database requirements.

Result: The survey revealed (1) the potential users of this database, (2) the excipients' toxicity and safety information needs, (3) the content and structure preferred for the database. Majority of respondents favoured the development of STEP database and reported that it would be a valuable resource.

Conclusion and future work: The survey emphasized the need for STEP database and thus leads us to development of pilot database to assess the feasibility of developing such a database.

1. Background

The demand for paediatric data on the safety and toxicological parameters of excipients has grown considerably over the last couple of years. This is, in part, due to recent changes in the legislative and regulatory requirements of both Food and Drug Administration (FDA) and European Medicines Agency (EMA) (FDA, 2006; EMA, 2008). It is important to point out that the generation of juvenile animal toxicity data should be considered when previous animal and human safety data are judged to be insufficient to support paediatric trials and Pharmaceutical companies now need to justify the use and safety of excipients in paediatric formulations.

It is generally acknowledged that excipients used in adults cannot always be assumed to have the same effect, or lack of effect in children. Moreover effects may vary between different age groups within the paediatric population. The differences in the effects of the excipients are due to changes in the developing child. Excipient metabolism, for instance, may be affected by changes in the maturity of the liver and kidneys. Neonates, for example, taking Kaletra oral solution, especially those born prematurely, were at risk of ethanol and/or propylene glycol toxicity (FDA, 2011). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations of propylene glycol. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. A number of research groups have provided estimates of excipient exposure in preterm neonates using prescription records. However, there is little systematic data about excipient exposure, which is a prerequisite for a safety assessment. There are well-documented cases where the use of excipients in children has led to severe adverse

* Corresponding author at: Department of Pharmaceutics and Centre for Paediatric, Pharmacy Research (CPPR), UCL, School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom. Tel.: +44 2077535846; fax: +44 2077535942.
E-mail address: Smita.Salunke@pharmacy.ac.uk (S. Salunke).
[1] On behalf of the European Paediatric Formulation Initiative (EuPFI).
[2] On behalf of the United States Pediatric Formulation Initiative (US PFI).

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effects (Fabiano et al., 2011). Even where there are reliable safety data for adults, difficult issues arise with children in determining safe dosage limits of a product in children of varying ages. The safety of excipients in children is not well researched. Patel et al. (2011) highlighted that more research is needed into alternative safe excipients for children such as natural polymers (e.g., cyclodextrins to mask taste of drugs, improve solubility or absorption). Whittaker et al. (2009) noted that although foetuses appear to use sorbitol as an energy source in utero, little is known about the sorbitol disposition after birth.

One of the main reasons is that until now paediatric drug development was not considered an integral part of drug development. It was often assumed that appropriate doses for children of different ages could be derived by simply scaling down adult dosage by age or weight. The other reason is that during the past two decades, regulatory allowances of an excipient occurred only through the use of excipient in drug product formulation. Hence, with the approval came the acceptance of the excipient (the excipient per se was not approved but the use was allowed). Less attention has been devoted to the safety of excipients, because their inertness and innocuity were taken for granted. Due to lack of specific regulatory guidance, many established and Pharmacopoeial listed excipients are not accompanied by strict standardized assay methods and have not undergone rigorous toxicological assessments. A general lack of knowledge of excipients has proved an effective barrier to the development of novel materials, and pharmaceutical manufacturing companies have tended to opt for using well known, but not necessarily safer, excipients. The presence of well-established excipients in a new drug formulation does not necessarily mean that regulatory authorities will not question their inclusion. Problems can arise when the currently available data suggest that there may be potential toxicity concerns, especially when an excipient approved for one route of administration is applied to another route with a different systemic exposure. In other words, for new drug development purposes, if an excipient was used in a previously approved medicinal product for a particular route of administration, it is likely to be deemed safe only when included in a new product with the same route of administration and level of exposure. Mannitol, for instance, is a typical "active excipient", which causes diarrhoea if administered at high doses, and therefore a quantitative evaluation should be done for each new product containing this substance (Adkin et al., 1995). In general, non-clinical and clinical studies are needed to demonstrate the safety of a new excipient before its use, not only because of regulatory requirements. In fact, they can affect drug delivery leading to improved efficacy and even increased safety (Baldrick, 2000). In this context, the US FDA provided a guidance document for industry on the conduct of non-clinical studies for the safety evaluation of new pharmaceutical excipients (FDA, 2005).

The lack of specific regulatory guidance to assist in the development of new excipients led the International Pharmaceutical Excipients Council (IPEC), an industry association which champions excipients) to publish safety evaluation guidance (IPEC, 1997; Steinberg et al., 1996). In the US, the IPEC-Americas safety committee has published a guideline for the safety assessment of new excipients, which has been published (USP, 24-NF 19). In addition, FDA has published a database of inactive ingredients in drug approvals (updated quarterly) (FDA, 1996).

In Europe, Council Directive 75/318/EEC states that the toxicology and pharmacokinetics of an excipient used for the first time shall be investigated (European Commission, 1975). The EMA guideline on excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (EMA, 2007), mentions a full safety evaluation without specifying details. In addition, IPEC-Europe has published a safety assessment guideline similar to that of IPEC-Americas. These safety assessment guidelines can be used to determine the extent of the toxicology testing program for an excipient.

Information on "approved" excipients in Japan has been published (JPEC, 1996). Various recent textbooks also contain information on the regulatory status of some excipients (Rowe et al., 2003). In 1999, a paper relating to considerations for safety evaluation of new excipients in Japan was published and includes studies on acute, subacute, and chronic toxicity, mutagenicity, and effects on reproduction and carcinogenicity (Uchiyama, 1999). The Pifferi/Restani paper of 2003 followed a 1999 paper describing the need for standards of characterization and quality review, just one more aspect needed for a regulatory framework for excipients (Pifferi and Restani, 2003).

Although the increased attention to excipients has followed with more academic and industrial activity in this area, published literature on excipients has greatly lagged behind. Although the industry has benefited handsomely from the seminal book, Handbook of Pharmaceutical Excipients, there is little published literature on use and safety of excipients in paediatrics. The available information is scattered over various sources and is of variable quality. Depending on the type of pharmaceutical and the knowledge already available, all or some of these areas will have to be assessed by conducting the corresponding studies. It is important to design a scientifically justified programme of investigations addressing all areas of identified or presumed safety concerns. Such an evidence-based approach of toxicity assessment of excipients that provides all the necessary safety information with the least possible amount of testing makes economic sense. The value of including older studies (not in accordance with up-to-date guidelines and not performed under GLP conditions) is questionable. In such case, bridging studies or new studies may be needed if there is cause for concern from the older literature.

The uncertainty factor will be reduced as the evidence base for safety and toxicity of excipients is improved and expanded. Regulators would be able to set higher safety levels for children than those for adults if they had compelling evidence showing such action to be appropriate and protective (i.e., data on children, or data from a reliable animal model that can be standardized, validated, and shown to be relevant to predicting effects in children).

Consequently, there is an acute need for a single repository to capture, archive, validate, manage, maintain and provide access to safety, tolerability and toxicity data that have been generated for excipients available world-wide for paediatric drug development.

In order to address this need, the European (Eu) and United States (US) Paediatric Formulation Initiatives (PFIs) are working together to create and maintain a database of Safety and Toxicity of Excipients for Paediatrics (STEP). The general motivation for development of the STEP database is to help identify the gaps in the excipient knowledge by gathering available data to enable evidence base assessments of excipient use.

The purposes of the STEP database are:

1. To serve as a freely/publicly accessible evidence base for safety and toxicity of excipients for the pharmaceutical industry, academics, pharmacists clinicians and regulators to make informed decisions.
2. To enhance the prospects for identifying potential safety issues at the initial stages of the development process, when excipients are being screened and selected.
3. To help highlight any relationship between exposure and evidence of clinically significant toxicity in the paediatric age group as a whole, or in paediatric subpopulations.
4. To identify possible differences in expression, types or patterns of toxicity in children compared to adults, To provide a basis for assessing the need for generating new data for paediatric medicines (e.g., bridging studies, juvenile toxicity studies, etc.),

in order to clarify what kind of new data, gaps in knowledge or studies may be required.
5. To support companies with their regulatory filings with readily available information.
6. To support and enhance research activities by providing a platform to share the unpublished data and data available with corporate entities.

The objectives of STEP database is: to conduct a high-level ongoing scientific literature review of the pharmacology, toxicology and safety data of a prioritized group of excipients likely to be used in paediatric formulations in order to

1 To provide a firm foundation and broad resource base for medicine development generally and ultimately highlight the gaps in excipient knowledge.
2 To provide free on-line access using a simple tabular format and user tools to support layperson use.

A key to the development and "buy in" from stakeholders and potential users of any database is their engagement in the needs assessment and planning stages. An international detailed user profile analysis (survey) was performed to determine how much interest there would be in such a database, the potential users of this database, their excipient toxicity and safety information needs, the barriers they face in accessing that information, the minimal data elements that would be most useful for the database, and, most important, determine the value of a STEP database. The survey was aimed to clarify and set a strategic and realistic direction to meet the needs of current and potential future users.

This paper documents the procedures used for identifying the needs of potential users in relation to safety and toxicity information of excipients and list a minimal set of data elements. It presents the results of the need for such database according to the views of experts and potential users.

2. Method

2.1. Survey design

This study used an online survey to determine the paediatric excipient database structure that best satisfied the needs of potential users, and to provide their views on the utility of the development of this database as a single online source and its potential content.

2.2. Target population

As the STEP database will be freely accessible online and will be designed primarily for use by professionals in paediatric drug development, the potential users included formulations scientists at pharmaceutical companies and academic centres, excipients manufacturers, pharmacists, developmental toxicologists, paediatric toxicologists, paediatric pharmacologists, clinical trialists, healthcare workers, environmental scientists and regulators. Although the type of safety and toxicity information needed by each of the different groups will differ, they provide a framework from which to explore information needs, current strategies for finding information, and potential use of the database. The survey was advertised on the Eu and US PFI websites and a number of organizational/associations websites, and mailed to key contacts in professional associations within Europe and United States.

2.3. Procedure

A questionnaire was placed on the EuPFI website for 6 months beginning July 2010. Notification of a survey appeared as a 'pop-up message' when users accessed the EuPFI website. Eu–US PFI members were asked to nominate contacts who had relevant paediatric drug development expertise within Europe and United States and the survey was then mailed directly to them. Completion of the questionnaire was voluntary, and no incentives were offered for completion. Information about the purpose of the study was available on the website.

2.4. Questionnaire

A questionnaire was developed jointly by the Eu/US PFI and trialled with a small group of health care and product development professionals. A few minor changes were then made to the questionnaire prior to being placed online. The questionnaire obtained information on participants' country of origin, main practice role, how they currently located safety and toxicity information of the excipients for paediatric medicine development, their views on development of this database as a single online source, its content, format, and frequency of use of other information sources. To obtain feedback on certain features proposed for the STEP database, questions were asked about the usefulness of having: (1) a database with fields relevant to safety and toxicity of excipients for paediatrics; (2) a structured/tabulated format with an advanced search facility. The questionnaire also asked about users' support in the development of this database, and users' preferences for future additions to database.

The questionnaire contained 15 questions (Appendix A). A mix of closed and open questions were used. The majority of closed questions used dichotomous or multiple fixed-response categories. Where appropriate, the categories 'don't know' or 'other (please suggest)' were included. The questions and response categories were designed to provide two types of measurements: nominal (i.e., those identified by named categories) and ordinal (those which ranked differences in reply, for instance on a scale between 'mostly preferred' and 'least preferred'). The questionnaire concluded with an open ended question inviting suggestions or comments about the database.

2.5. Data analysis

Analysis focused on three main areas:

1. The background of the survey population as a whole, and of subgroups, such as profession and geographical region of practice.
2. Patterns of needs and opinions for the survey population as a whole, with respect to use of safety and toxicity information in general, and views on the development of the STEP database.
3. Relationships between variables to examine to what extent one variable was influenced by another.

3. Results

3.1. Questionnaire response rate

Although it was anticipated that health professionals and product development professionals would be the main target group for the survey, anyone who accessed the website during the study could participate. Over the 6 month, 287 people accessed the survey, out of which 247 completed the survey, resulting in a response rate of 86%.

Table 1
Main role of respondents ($n = 247$).

Role of respondents	No. (%)
Health care worker	104 (42.1)
Pharmaceutical development/Formulation scientist	55 (22.3)
Clinical trial investigator	22 (8.9)
Regulatory affairs	19 (7.7)
Toxicologist	16 (6.5)
Librarian, Information specialists	11 (4.5)
Drug safety/Pharmacovigilance officers	9 (3.6)
Parents/Carer/Patient representative	6 (2.4)
Other clinical scientist	4 (1.6)
Other preclinical scientist	1 (0.4)

3.2. Demography of the response group

Respondents were from 27 countries, with the highest proportions being from the UK (66%), USA (10%), Germany (4%), Switzerland (3%), Australia (3%) and Belgium (3%). Most respondents (42%) were from the health care profession (see Table 1) followed by formulation scientists (22%). This can be attributed to the fact the heath care worker category is represented by a wide range of job functions.

There was almost equal distribution between clinical trial investigators, toxicologists, information specialists and regulatory affairs personnel (9%, 7%, 5%, and 8%, respectively). Job functions which were poorly represented were preclinical/clinical scientists, and parents/patient representatives. The low percentage can be attributed in part to difficulties in contacting the representatives or advertising the survey to this population. Also, it is possible that very few individuals from parents/patient representatives/associations would be motivated in respect to the subject matter of the questionnaire.

3.3. Use and purpose of excipient safety/toxicity information

The questionnaire asked respondents about their research and work background, in order to assess the role of excipient safety information in relation to the respondent's research/work and the way in which the individual would be using the information.

The majority of respondents (41%) needed to access the safety and toxicity information of excipients occasionally (less frequently), with 28% accessing it rarely (monthly). Only 29% need it frequently (daily/weekly). Respondents' main reasons for access to safety and toxicity information were for clinical assessment and patient care (43%), research and development purpose (25%), teaching/education purpose (14%) and information for regulatory affairs/filings (11%). A small proportion used the information for retrieving the information for others (5%) and for community and advocacy purpose (2%) (Table 2). Some respondents had other reasons, including: toxicological studies, clinical/epidemiologic research, to advise on choice of medication if patient had a previous adverse reaction to an excipient, queries for specific patients, poison information and for personal use.

Table 2
Reasons for access to safety and toxicity information.

Reasons for access to safety and toxicity information	% of respondents
Research and/or Development	24.7
Clinical risk assessment and patient care	43.2
Teaching/Education	13.9
Community/Advocacy	1.9
Regulatory affairs	10.6
Retrieve information for others (e.g., library searching)	4.6
Other (please specify)	1.1

Table 3
Preferred source of safety and toxicity information.

Preferred source of information	% respondents
Use the Internet (which is the main source(s) you use? Please specify)	18
Use your Library	16
Use internal Databases	16
Consult a colleague	17
Use Information Services	16
Contact Professional Society	14
Other (please specify)	4

3.4. Locating research evidence and use of other databases

The questionnaire probed the broad patterns of how respondents located and acquired information. Such information is useful because database development would be based on assumptions about the kinds of sources which respondents prefer to use, and how they currently obtain information (in particular whether they use the available databases). Furthermore, with the general increase in the range and scale of information available, there is concern as to whether respondents are able to obtain all the information relevant to their field(s) of study.

Respondents were asked (Question 6) how they would typically obtain excipient safety and toxicity information they require and their preference of the source of the information.

The distribution represented in Table 3 shows almost an equal preference for the different options of information sources provided to the respondents. Only 4% of respondents stated that they would look into other sources such as asking their pharmacists, using the pharmacy medicines information helpline, contact manufacturers, or using a specific database such as Micromedex, Toxbase, etc.

Most (59%) often needed to refer to multiple sources of excipient safety and toxicity data for paediatrics. Only 5% of respondents stated they never needed to refer to multiple sources as they asked their pharmacists or used information services at their workplace.

3.5. Need of the STEP database

When asked if it would be valuable to have access to a single online source where all safety and toxicity information would be available for excipients likely to be used in paediatric medicine development, the respondents were clearly in the favour of such a database (Fig. 1).

Only 2% said they did not feel the need to have a STEP database as it was not relevant to their roles.

3.6. Content and format of the STEP database

Respondents were next asked to comment on the content of the database and the type of information required for their work.

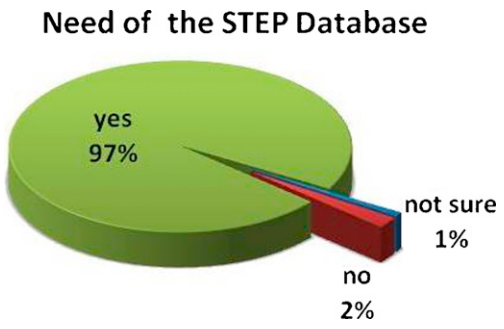

Fig. 1. The opinion on need of the STEP database.

Table 4
Comments on the content of the database.

Response to proposed data elements	Percentage of respondents
Happy with current proposed list	54.4
Additional element suggested	31.4
Not sure/don't know	11.3
Not applicable	2.9

Would they like to see more, just the same amount or less emphasis on particular elements and characteristics, as listed in Question 9? They were then asked 'what information has been most difficult to obtain, or not found to be available from existing sources' (Questions 9 and 10).

These questions allowed an open ended response. Responses were coded and grouped into broad categories for further analysis as shown in Table 4. The responses were then matched to assess the presence of any particular (unique) set of information required by particular group or category or country.

A high proportion of the respondents (54%) felt that the proposed data elements were sufficient and satisfied their needs, while 31% suggested additional elements for the database. There was no suggestion/desire for less information than listed, although 11% of the sample stated that they were either not sure or didn't know what more information would be needed and 3% stated the question was not applicable and they were not in the position to answer the question. This pointed out both the respondents' insufficient involvement in paediatric drug development, lack of experience in working with excipients for paediatrics and related issues with safety and toxicity, and possible selection bias which may have occurred due to the non-representative nature of the Internet.

Respondents were asked what type of information required for their work had been most difficult for them to obtain, or which was not available from existing sources. The majority of pharmaceutical scientists and health care workers stated that the following elements were most difficult to obtain information on:

physicochemical characterization,
acceptable excipients (and dose) for use in pre-term infants and neonates,
acceptable daily intake (ADI) for children (especially babies/young children), since much of the literature refers to adults,
information on safety and maximum daily exposure limits in different age groups, including preterm neonates and infants,
stability data,
exact amounts of excipients present in various medications and their exposure as well as safety in the paediatric populations especially in neonates.

Toxicologists and clinical scientists found it difficult to obtain the pharmacokinetic and toxicokinetic data that is specific to children.

Most respondents, irrespective of their roles, stated that information such as what excipients are used in formulations and their amounts in special/off licensed drugs was most difficult to obtain. It is very likely that the two factors that contribute to this fact are: (1) the proprietary nature of the product composition, and (2) the voluntary nature of the information, since quantifying inactive ingredients is not required by law.

When asked about the format of database (Questions 11 and 12) 67% of the respondents favoured structured/tabular format with advanced search facility (e.g., query builder), 17% preferred free flowing text format (literature citation with text/abstract summarizing the article) with basic and advanced search, and 16% requested other options such as combination of both the formats with a summary of key information upfront, did not prefer either of the format suggested, or preferred a Wikipedia style source with hyperlinks.

3.7. Future directions

The respondents were asked if they were interested in participating in the STEP database development in the future. The other options were 'maybe' and 'no'. It should be noted that these options are not exclusive, as respondents were allowed to select more than one.

Most respondents (62%) showed willingness to participate and support the STEP database development and either offered to participate by reviewing the prototype database (19%), to participate in the future surveys to evaluate the usability and validity of a prototype database (26%), to participate in the future database expansion (10%), to help in populating the database (7%), for example, by sharing or donating unpublished/in-house data, or offering help in other ways such as in retrieving and evaluating literature citations and in user testing (2%). 18% were not sure if they could offer help with the STEP database development and 18% were not able to participate in further activities of database development.

Further comments were invited from respondents on the STEP database development initiative. Comments expressed favour for the database; some respondents showed interest in the collaboration on this project.

4. Discussion

4.1. The value/benefits of having the STEP database

Toxicity data of excipients has been traditionally dispersed over a variety of databases where only a small fraction was available for paediatric drug development because the safety of excipients in not well researched in children. Recent efforts (e.g., from Istituto Superiore di Sanità (ISS), Fraunhofer Institute for Toxicology and Experimental Medicine (FhG ITEM), US Environmental Protection Agency (US EPA), US Food and Drug Administration (US FDA) Hazardous Substances Data Bank (HSDB)) have improved the situation, because they provide curated data that has been compiled from various sources (public testing programs, general literature, non-confidential in-house data). The transformation of the current developmental toxicology paradigm by the application of "-omics" technology will create the need to obtain excipient specific toxic genomics information. The information could be derived from large all inclusive databases (e.g., comparative toxicogenomics databases). Public repositories of bioassay data like PubChem provide additional information that can be utilised for toxicological risk assessment. However the databases developed by these institutes have different purpose and most importantly lack the paediatric information. Retrieving safety and toxicity information of excipients likely to be used in paediatrics is still difficult and has been proved by survey responses. It requires a considerable amount of time to refer to multiple sources and the search procedures are labour-intensive. In such a scenario, the STEP database would be a strong "value-added" project.

Respondents cited multiple benefits of having a database; being able to access documents in a single database could be a valuable time-saving tool, reducing efforts required to locate relevant sources, while increasing the availability of quality information and most importantly providing case studies/examples, which are perhaps the most common requests of those new to the paediatrics field. The concept of "information at your fingertips" is appealing to many users, particularly for comparative data. By encouraging the wider sharing of data, the STEP database could address the

need for greater transparency of information which is a limitation of the existing sources. For example, the Food and Drug Administration (FDA) database 'Inactive Ingredient Search for Approved Drug Products' (is widely used. It provides very limited information on excipients used in paediatric products. The STEP database will help uncover the areas, for which there is little information, e.g., safe limits on excipients. It could encourage research in excipients by highlighting gaps in excipients knowledge and may also move the scientific community towards a more data sharing.

4.2. Potential users of the STEP database and their information needs

It was revealed from the survey that the extensive data collected and presented in database format can be used in varying ways by different users to serve their needs. There was a fairly even distribution across respondents' purposes for using such a database, and across the types of information it should contain. The information provided by the STEP database would be useful in different departments at pharmaceutical companies, including clinical pharmacology, drug metabolism, regulatory, and preclinical toxicology. A trend/relationship was seen with the type of information needed and the function of the respondents. Pharmaceutical scientists need the safety and toxicity information for initial screening and selection of excipients. Regulators required additional information on safe limits of intake while health care workers were more interested in knowing the amount of excipients in the dosage forms and associated adverse effects and if an alternative excipient could be used. Toxicologists search databases for information on overdose risk and enhanced risk in various patient populations, using the amounts stated by the regulatory agencies as a guide and then in consideration of fundamental data in animal species. The information in the STEP database thus clearly would be of great value to a wide range of users.

Few respondents, however, did not find the proposed data elements sufficient enough in meeting their needs. Compatibility, interactions and physicochemical characterisation were the main additional elements which were of interest. Regulators' inclination was toward information in other regulatory references (i.e., if the excipient is specifically referenced in a guideline) and safety limits.

Some respondents expressed the need to include studies that report both the beneficial effects and adverse effects of interest. Reviews that focus mainly on treatment benefit, together with lack of information on harmful effects, would create difficulties for people who are trying to make balanced decisions. The respondents further explained that having studies that report beneficial and adverse effects in the database may have the important advantage that benefits and adverse effects can be compared directly, since the data are derived from the same population and setting. Furthermore, evidence on benefits and adverse effects arises from studies with similar designs and quality. However, data on adverse effects may be very limited and in particular may be restricted to short-term harms because of the relatively short duration of included studies. Evaluation of benefits and adverse effects using some combination of these studies would increase the amount and value of information available.

The unique elements which were not covered through the web survey but were highlighted by 'expert panel' responses included providing an alternative list of excipients if a particular excipient is known to show elevated risks in children, and providing the list of licensed paediatric products with excipients which have been safely used. It was stressed that all pharmaceutical manufacturers should list all their excipients and make this available to practitioners and drug information centres. Alternatively or additionally, the package insert could list these excipients. This disclosure and inclusion of these data in the database will help to determine the relative frequency and magnitude of problems (bioequivalence, toxicity, etc.) that excipients may have in the paediatric population and thus avoid inadvertent exposure.

The views of the respondents' purposes for using such a database and the type of information it should contain, helped to define the attributes of the database and differentiate between the type of information that should be included as part of a minimal data set (Fig. 2) and data/information that would be part of an expanded database.

4.3. Eu and US information needs

The similar responses for safety and toxicity information needs assessment illustrated that there was no obvious difference in the information needs between the Eu and US. The demands for the additional information such as physicochemical characterization, interactions, excipients presence/amount and concentration in the marketed products, and information on palatability and taste were raised by the both Eu and US respondents. Linking the database with already existing resources to avoid possible duplication of efforts was reiterated by the US respondents. For instance, some respondents from Australia, Eu countries and US reiterated that general information such as synonyms and Chemical Abstracts Service (CAS) number, is already available in from variety of databases (e.g., Handbook of Pharmaceutical Excipients, chemFinder, chemIDPlus) that exists in the public domain and compile the information such as physicochemical characterisation, compatibility and stability so having this information in the STEP will be a duplication. Respondents suggested that this information can be linked with already existing resources to avoid possible duplication of efforts.

4.4. Format for THE STEP database

Until recently, many existing public toxicity databases have been constructed primarily as "look-up tables" of existing data, and most often did not have the capability to retrieve data both in qualitative and quantitative terms. In addition, often the organization of the information followed that of the print literature, and did not lend itself easily to manipulation of data. One example is the National Toxicology Program (NTP), an on-line database reference (NTP database) that includes high-level detail on animal toxicity experiments for several thousand chemicals, but does not provide links to data sources, relational access to particular slices of the data, or aggregation of the data according to user requirements. Another such example is the Hazardous Substances Data Bank (HSDB), a factual data bank on the National Library of Medicine's (NLM) TOXNET (Toxicology Data Network) online system, which provides information in areas such as chemical substance identification, chemical and physical properties, safety and handling, toxicology, pharmacology, environmental fate and transformation, regulations, and analytical methodology. The data retrieved from HSDB being literature citations with text summarizing the article, needs to be examined to extract the required data. It does not fulfil the purpose of a specific database as it only provides an overview of information. The survey highlighted the need of the data mining capabilities (e.g., query builders) that can be used to perform more complex searches, by formulating queries where specific combinations of excipients, data and text are searched for in the database at the same time. Hence, one of the main goals of STEP database is to also organize the extracted data into a searchable structure with appropriate tools. The structured/tabulated format used to filter and aggregate the information would prove useful to stakeholders and other users who do not have the resources to distil such data on a case-by-case, ad hoc basis.

GENERAL INFORMATION
CAS No (PG : 57-55-6)
Synonyms (1,2 Propanediol)
Pharmacopoeial status (Ph Eur.)
Regulatory status (GRAS)
Functional classification (solvent, diluent, binder, preservative etc..)
HUMAN FIELDS
Demographic (age, gender etc)
Administration/Exposure (E.g., Route, dose, concentration, duration etc)
Safety/Tolerability/Adverse effects findings by organ/system (e.g. GI, CVS, respiratory, etc.)
Pharmacokinetics/ADME
PK/PD relationship (dose- concentration relationship)
Acceptable daily intake
NON HUMAN FIELDS
Age. Juvenile/Adult) Species (e.g. rat, mouse, dog, non human primates.)
Administration/Exposure (e.g. Route, dose, concentration, duration etc)
Toxicity findings by organ/system (eg. Genotoxicity, hepatotoxicity etc,)
Toxicokinetics
In Vitro Data

Fig. 2. Minimal data elements for STEP database.

4.5. Sharing data in the STEP database

Data contained in the STEP database would be collected from published literature available in various forms [peer reviewed, non-peer reviewed (government reports, industry studies, etc.) and in any language (where an English abstract is available)]. It was envisaged that depending on the interest of the various stakeholders, the future might bring an extension of the database beyond the "available and published literature", a possible sharing of non-confidential in-house data by manufacturers and companies. Most respondents expressed views on data sharing and transparency. A large amount of extremely valuable knowledge on toxicity is not in the public domain. Toxicity data acquired during drug development is not routinely published or shared in public databases owing to the confidential nature of the research that generates the data. Many respondents from the Eu and US stressed that users should benefit by having access to safety assessments conducted by other companies and suppliers that are currently kept private. If data sharing is encouraged then all companies will have easier access to the information that will help them make the best decisions about product safety. In fact, the European Innovative Medicines Initiative (IMI), a public–private partnership of the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), launched a call for a project to be funded to achieve this goal of data sharing and building of new in silico safety models (Briggs et al., 2012). The main objectives of this project are: to identify and implement ways for data sharing while safeguarding intellectual property; to build a harmonized toxicological database for the development of predictive models. Also, Lhasa Limited, a not-for-profit, charitable organization that exists to promote the sharing of data and knowledge in chemistry and life sciences has developed the Vitic Nexus software, a chemically intelligent toxicity database, to facilitate such sharing. In the big picture, the STEP database may benefit users by increasing the flow of information to businesses and consumers. However, efforts may be required to finding a suitable way of sharing proprietary data in the STEP database, which will allow the users access to a much larger data pool and prevent the repetition of a number of toxicity studies. In fact, one of the questions in the survey asked users if they would be willing to participate in the STEP database development activities by sharing/donating the toxicology data and the controls from unpublished studies. A positive response from some respondents has given a good starting point for collating such information.

4.6. Issues in the STEP database development

Although respondents reported that the STEP database has potential benefits, they raised several issues that would have to be

resolved before such a resource could be developed. These concerns relate to the feasibility of the database itself, including development of the database and maintenance infrastructure, procedures for data collection and evaluation, and development and maintenance costs.

Respondents expressed concerns about the complexities of database development and maintenance, especially with respect to the development of database schema, tasks of gathering and properly evaluating existing toxicity reports and resources for relevance and quality. Some of the data integration issues have already been addressed by other initiatives, e.g., ECB QSAR Model Reporting Format, DSSTox, ToXML, InChI, whereas, some aspects of data quality were mentioned by Klimisch et al. (1997). However although these approaches solve some technical aspects of data integration and evaluation with respect to non-clinical data, none of them provides an architecture for compiling or evaluating the quality of clinical data. The survey helped to define data entity and attributes of the database which in turn will help to draw the database schema to meet the specific requirements of the users.

In a classic article on the work of information professionals, Mason (1990) wrote that the goal was "to get the right information from the right source to the right client at the right time in the form most suitable for the use to which it is to be put and at a cost that is justified by its use" (Mason, 1990). The findings of this needs assessment corroborated this, near-mantra, for the STEP database development. According to respondents, the "right" information must be accurate and applicable to the need at hand, while the "right" source was one that was both reliable and readily accessible. The STEP database would act as a central registry for the collection and archiving of quality data, and thus a way of reducing cost by avoiding duplication of effort and assisting in the dissemination of information. Such a repository of data would facilitate the paediatric formulation development, and ultimately highlight gaps in excipient knowledge.

5. Limitations

Limitations need to be considered when interpreting the results of this survey. It is well recognized that online surveys using a convenience sample are prone to bias, due to the self-selection of participants. This survey targeted known contacts who were asked to advertise the survey within their institutions and network. So the majority of respondents were health care workers but the representative cross section of the contacts nominated by EuPFI further extends the external validity of results.

The further limitation of the study is that the characteristics of non-responders are unknown.

Despite these limitations, this needs assessment exercise was considered the most practical way to obtain international feedback and an appropriate method to assess the need for the STEP database. This web-based survey provided information regarding potential users and their needs for safety and toxicity information of excipients to be used in paediatric drug products.

6. Conclusion

There are many toxicity databases currently in use. Even though most of them incorporate toxicity data from similar sources, there are unique characteristics and features of these databases that reflect their individual functions. Potential users within the government, academia, pharmaceutical industry and private institutions emphasised the necessity of developing and designing a database

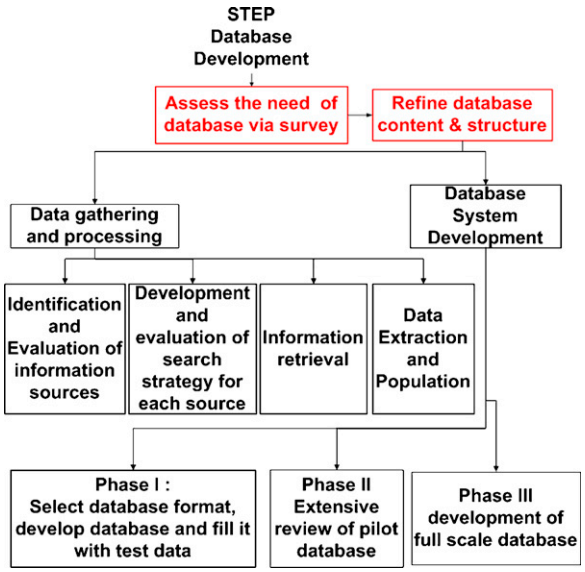

Fig. 3. Flowchart for STEP database development.

of safety and toxicity information of excipients which are likely to be used in paediatrics. Because the development of a database is a costly and time consuming venture, it is important to identify at an early stage those features that will serve the specific needs of the potential database users.

The survey aimed to clarify and set a strategic and realistic direction to meet the needs of current and potential future users. Being an elaborative task, the database structure will follow a modular model. The initial step will involve creation of a minimal database module to which other components could be added later on. The initial requirement analysis (survey) helped to define and differentiate between the type of information that should be included as part of a minimal data set and data/information elements that would be part of an expanded database. The survey results and the open ended responses provide ideas on database content and user groups as well as concerns about duplication of efforts. Overall it provided a good basis for decision making and developing a strategy of the STEP database project.

In summary, there is a need for the STEP database development and the database would be an extremely beneficial tool to those involved in development and use of medications for paediatrics, as there is interest across multiple potential user groups.

7. Recommendations and next steps

Given that many toxicity databases have been in operation for some time, the potential exists to learn from past experiences in developing, launching and maintaining the databases. This will not only provide a starting point for the STEP database development, but will reduce duplication of effort. Other database developers are willing to share the knowledge they had gained from the needs assessment and database creation processes.

Given the survey respondents' emphasis on this latter point, an important move for the STEP database is to widen the scan of similar databases to determine if there are any already in existence that meet the STEP database goals. There may be potential for shared resources, linkages, or building on an existing model.

Considering the issues and concerns expressed by the respondents, the scope and coverage of the database will be implemented over time, in phases. The current short term goal will be to develop

a prototype database with proposed minimal data elements based on the users' needs. A longer term goal would be to extend this prototype database incrementally: to include several high priority excipients, to collect initial feedback from users for refinement, extend the database to more excipients, and maintain the finalized database.

The next stages of the project will be focussed on the development of innovative strategies and methodologies for gathering the data on adverse effects of excipients, and the extraction of specific information into database and development of the application itself as summarised in flowchart (Fig. 3). The stages highlighted in red are discussed in this paper and further articles in this series will discuss in detail the issues and challenges towards the development of the STEP database, strategies used to overcome those issues, the strategy for data selection and handling and discuss the methodology for developing the STEP database application and demonstrate the development of the pilot STEP database.

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Appendix A. Questionnaire and Information posted on website and emailed to 'experts panel' for assessing the need of STEP database

Question 1: Which of the following match your role function (s)?

Pharmaceutical development/Formulation scientist
Toxicologist
Other preclinical scientist (please specify)
Clinical trial investigator
Drug safety/Pharmacovigilance officers
Other clinical scientist (please specify)
Health care worker
Parents/Carer/Patient representative
Librarian, Information specialists
Regulatory affairs
Other (please specify)

Question 2: Which of the following most closely matches the organization you work in?

Government
Industry
Academia
Healthcare
Other (please specify)

Question 3*: In which country do you work?

Question 4: Do you need access to excipients toxicity and safety information?

Yes, daily
Yes, weekly
Yes, monthly
Yes, less frequently
Never

Question 5: The information regarding the safety and toxicity of pharmaceutical excipients can be used in many ways. Please check the main reason (s) why you use this information.

Research and/or Development
Clinical risk assessment and patient care
Teaching/Education
Community/Advocacy
Regulatory affairs
Retrieve information for others (e.g. library searching)
Other (please specify)

Question 6: How would you typically obtain the excipients safety and toxicity information you need? Rank 1–6, with 1 being what you would do first?

1 2 3 4 5 6

Use the Internet (which is the main source(s) you use? Please specify)
Use your Library
Use internal Databases
Consult a colleague
Use Information Services
Contact Professional Society
Other (please specify)

Question 7: Do you have to refer to multiple sources to get the necessary information?

Yes, often
Yes, sporadically
Never

Question 8: In your opinion, would it be valuable to have access to a single online source where all safety and toxicity information is available on excipients likely to be used in paediatric medicine development?

Yes
No

Question 9*: Our initial approach would be to have a minimal database with the potential to expand with more information in later phases. The data elements listed below would be included as a part of this initial minimal database.

What other information would you like to be included as part of a minimal data set?

General information:

1. Chemical Abstract Number (Cas No) – universally accepted identifier for compounds
2. Synonyms
3. Physicochemical excipient characterization (e.g., viscosity, pH, etc.) – required for practical formulation development
4. Pharmacopoeial status – data standards on excipients as per relevant pharmacopoeia (e.g., Eu Pharmacopoeia)
5. Regulatory status – Quality information achieved through testing or other regulation specified provisions and determined by governmental guidance and organisational standards (e.g., GRAS

ratings indicate level of safety, level of abuse potential of chemical)
6. Functional classification – e.g., solvent, sweetener, colouring agents, preservatives, etc.

Human field

1. Demographic (age, gender, etc.)
2. Administration/Exposure (e.g., route, dose, concentration, duration, etc.)
3. Safety/Tolerability/Adverse effects findings by organ/system (e.g., GI, CVS, respiratory, etc.)
4. Acceptable daily intake – safe intake level based on current research

Other information

a. Pharmacokinetics/ADME – What body is doing to the excipient; how it is absorbed/distributed/metabolised and excreted from the body
b. PK/PD relationship – links the body's exposure to the excipient and the effect it is having on the body

Non-human field

1. Age (e.g., Juvenile/Adult)
2. Species (e.g., rat, mouse, etc.)
3. Administration/Exposure (e.g., route, dose, concentration, duration, etc.)
4. Toxicity findings by organ/system (e.g., genotoxicity, hepatotoxicity, etc.)
5. Dose information (e.g., maximum tolerated dose, lethal dose, no observed effect level, etc.)
6. In Vitro Data

Other Information

a. Toxicokinetics – pharmacokinetics determined in animals

Question 10: What type of information required for your work has been most difficult for you to obtain or not available from existing sources?

Question 11: In what format do you prefer to see the information in this database?

Free flowing text (literature citation with text/abstract summarizing the article) with basic search facility
Structured/tabular format with advanced search facility (e.g., query builder)
Other (please specify)

Question 12: Are you interested in participating in the development of this single online source?

Yes, by reviewing the prototype database
Yes, by offering help in populating the database, e.g., by sharing or donating unpublished/in-house data
Yes, by participating in further survey(s) to evaluate the usability and validity of a prototype database
Yes, by participating in future database expansion
Yes, other (please suggest)
Maybe
No

Question 13*: Please provide your e-mail address below.

Question 14: Are you happy for us to follow up on any of your responses from this survey?

Yes
No

Question 15: I would like to make the following comments/suggestions.

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